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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	17

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
08/844,215	PERSSON ET AL
Examiner	**Art Unit**
Mary K Zeman	1643

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *06 July 1999* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-116* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 82-116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-33,48,56 and 65-81* is/are rejected.

7)☒ Claim(s) *33-47,49-55 and 57-64* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____
17) ☐ Interview Summary (PTO-413) Paper No(s) __ __
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other

DETAILED ACTION

Claims 1-116 are pending in this application. Claims 1-30 and 82-116 have been withdrawn from consideration as being drawn to a non-elected invention.

This application contains claims 1-30 and 82-116 drawn to an invention nonelected without traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's arguments filed 7/6/99 have been fully considered but they are not completely persuasive.

1. Claims 31-33, 48, 56 and 64-81 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wong and Mehta, in view of Hoogenboom and Chanock for the reasons set forth in the previous office action.

Claims 31-33, 48, 56 and 64-81 are drawn to isolated nucleic acid sequences encoding a human Fab fragment which binds to a HCV E2 antigen, vectors and host cells comprising those sequences, and methods of producing the recombinant protein.

Applicant requested clarification of the priority of the references as applied in the rejection. The Examiner submits that the issues are clearly set forth in the reasoning in support of the rejection, such that rewording of the rejection is not necessary. As it has been well established, the order of the references in the rejection does not materially affect the strength of the rejection. *In re Bush*, 296 F.2d 491, 131 USPQ 263 (CCPA 1961). "In a case of this type where a rejection is predicated on two references each containing pertinent disclosure which has been pointed out to the applicant, we deem it to be of no significance, but merely a matter of

exposition, that the rejection is stated to be on A in view of B instead of on B in view of A, or to term one reference primary and the other secondary. It would perhaps have saved much argument of the kind we have before us if the Patent Office had stayed with its rejection of the claims as unpatentable over A and B "considered together" and had merely stated its reasons for such rejection without formal alignment of the references. Fifteen years ago this court pointed out in *In re Cowles*, 33 CCPA 1236, 156 F.2d 551, 70 USPQ 419, that such differing forms of expression did not constitute different grounds of rejection, were of little consequence, and that basing arguments on them was "attempting to make a mountain out of a mole-hill."

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Hoogenboom (WO 93/06213) sets forth methods for the production of recombinant human monoclonal antibodies. These antibodies are produced by a combinatorial library approach, and selected through immunoassays. These techniques make it possible to isolate high affinity and/or neutralizing antibodies to various viral antigens. The sequences encoding the isolated Fab fragments can then be isolated, sequences and used in various expression vectors and systems for recombinant expression of the desired human Fab.

Chanock (Chanock et al 1993 Infectious agents and disease 2:118-131) teaches the desirability of human monoclonal Fab fragments, as well as the usefulness and benefits of using the recombinant human monoclonal Fab fragments which have been cloned from a combinatorial library in the treatment or prevention of viral diseases. Chanock cites many references which disclose the technology useful in creating human monoclonal antibody Fab fragments. Applicant argues that Chanock is vague, however the Examiner would submit that this is a review type article discussing the benefits and usefulness of such Fab fragments, and is not concerned with the technology.

Wong is relied upon as evidence that the monoclonal antibodies against E2 were desirable and would have potential use in the treatment and/or prevention of HCV infection. Wong (Wong et al 1995 J Investigative Medicine 43 (2) supplement 2 p 397A) teaches that monoclonal antibodies to the E2 protein of HCV prevent penetration of the virus into its target cells. This indicates that monoclonal antibodies to the E2 protein could have significant impact on the treatment of and the prevention of HCV. The finding of Wong is significant as it is the first disclosure of the ability of monoclonal antibodies to the E2 protein of HCV to block the penetration and entry of the HCV virus. Wong provides a clear motivation to create human Fab fragments in order to test the same theories in human situations.

Mehta is relied upon as evidence that the monoclonal antibodies against the E2 protein existed, and had uses in immunoassay protocols at the time the invention was made. Mehta (US Patent 5,308,750) discloses mouse monoclonal antibodies to the E2 protein of HCV. Mehta discloses the usefulness and importance of these antibodies. Mehta provides a clear motivation to

create human monoclonal antibodies against E2, as he shows that there is no difficulty in obtaining monoclonal antibodies to that antigen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned and identified sequences encoding human Fab fragments specific for the E2 protein of HCV from a combinatorial library through the methods of Hoogenboom and to have further cloned these sequences into appropriate expression vectors for the purposes of recombinant expression of the Fab fragments as set forth by Chanock. Both Mehta and Wong disclose that monoclonal antibodies against E2 can be made and identified, and and both provide motivation to do so. One would have wanted to produce these human recombinant monoclonal Fab fragments, because Chanock had discloses the usefulness of recombinant human Fab fragments in treatment and prevention of viral diseases, the findings of Wong further attest to said usefulness as the monoclonal antibodies against the E2 protein had been shown by Wong to prevent the penetration of HCV into target cells.

Claim Rejections - 35 USC § 112

Claims 31-33, 48, 56 and 64-81 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth amino acid sequences of various VL and VH regions, some specific nucleotide sequences encoding those sequences and equivalent degenerative codon sequences

thereof and therefore the written description is not commensurate in scope with the claims drawn to nucleic acid molecules encoding any naturally occurring VH and VL polypeptides which bind to HCV E2.

Applicant argues that the case law cited differs on its face from that of the instant disclosure, however fails to provide the differences. The generic claims of the invention are not supported by the specification as filed, as set forth previously.

As set forth previously, *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Antibodies to particular antigens are generated by the immune system through random mutation and recombination. (See Kuby, Immunology, Second Edition 1991 WH Freeman and Company, NY Chapter 8 pages 175-204) The immense variety of the variable regions of antibodies defies prediction of particular nucleic acid sequences. With the exception of the SEQ ID Nos setting forth *particular nucleic acid* sequences, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, *regardless of the complexity or simplicity of the method*

of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by *only their functional activity* (i.e. binding to a particular antigen) does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for other nucleic acid sequences encoding VH or VL regions of human antibodies is provided in the specification on page 6, lines 20-25 where it is disclosed that "In another embodiment, the invention is directed to an isolated nucleic acid molecule which contains a polynucleotide coding sequence for a polypeptide that is homologous to the binding portion of a human Fab molecule which exhibits immunological binding affinity for HCV E2 antigen." However, no disclosure, beyond the mere mention of other polynucleotide sequences encoding said Fab fragments is made in the specification. This is insufficient to support the

generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated DNA molecule comprising a DNA sequence consisting of the specific polynucleotide sequences disclosed in the specification (SEQ ID NO:s 15-27), but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Conclusion

No claim is allowed.

Claims 33-47, 49-55, and 57-64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner, can be reached on (703) 308-1032.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
September 20, 1999

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
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